REMARKS

Restriction Requirement

The Examiner contends that claims 1-6 and claims 7-54 are related as process and apparatus for its practice, and the inventions are distinct because the process as claimed can be practiced by hand. Applicant submits that the Examiner's assertion is not reasonable. The Examiner responds in the instant Office Action that such assertion is reasonable in view of the teaching at page 2 to page 6 and Figure 5. Applicant respectfully disagrees.

The present invention provides the making and using of expression miniarrays – a novel category of biosensors that are intermediate in size, cost and ease of use between microarrays and macroarrays. Page 2 to page 6 teach the making of macroarrays and microarrays. Common laboratory macroarrays are usually hand made and only contain a few dozen spots per array, whereas microarray is a highly miniaturized, high density format that is expensive to make.

The present invention, however, is not drawn to the making of macroarrays or microarrays. The miniarray of the present invention contains hundreds or thousands of assay spots (see Figures 2-3; page 24, line 21 to page 25, line 2; page 42, lines 3-11), not a few dozen spots per array. It is reasonable to make a few dozen spots per array by hand. But it is not reasonable and practical to make hundreds or thousands of assay spots by hand. Similarly, it is not feasible to make highly miniaturized, high density microarray that contains thousands and thousands of assay spots by hand.

Figure 5 is meant to demonstrate using pipetters to load and dispense microliter and nanoliter quantities of reagents respectively by capillary action. Figure 5 is not an embodiment of the present invention. It only shows an array with a dozen assay spots, whereas the miniarray of the present invention contains hundreds or thousands of assay spots (see Figures 2-3; page 24, line 21 to page 25, line 2; page 42, lines 3-11). Applicant reiterates that it is not reasonable and practical to make hundreds or thousands of assay spots by

hand. Even though one could pick up a high quality pipetter and attempt to duplicate the operation of machine manufacture, the results will be crude and irregular. Applicant respectfully submits that no company could reasonably hand manufacture multiple expression miniarrays containing hundreds of gene probes as described in the present invention that would provide reliable consistent diagnostic data.

Applicant avers that the Examiner has not provided reasonable examples that recite material differences between the apparatus and the process. The Examiner's assertion that the claimed processes could be performed by hand is not reasonable and it flies in the face of the value, purpose and operation of the subject invention. Applicant submits that the claims are not independent. The claims are substantially connected in design, operation, or effect under the disclosure of the particular application under consideration. Claims 1-6 recite the apparatus for forming the miniarrays; claims 7-22 describe the process of employing the apparatus to make these expression miniarrays; claims 23-54 are drawn to using the miniarrays in methods of diagnosis. Accordingly, Applicant respectfully requests that the restriction requirement be withdrawn and claims 1-54 be rejoined for examination.

Specification

The specification has been amended to recite the full names of the references in lieu of the numbers.

The Examiner contends that the U.S. Patent No. 6,001,309 recited on page 5, line 15 does not exist. Applicant respectfully disagrees. Applicant obtains information on U.S. Patent No. 6,001,309 from the Patent Office website and the patent was issued on December 14, 1999. Hence, Applicant submits that reference to U.S. Patent No. 6,001,309 recited on page 5, line 15 is correct.

The 35 USC §112 Rejections

Claims 7 and 9-22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

Claim 7 is rejected for omitting essential elements such as a mechanical pump or piston. Claim 7 has been amended to recite a pipette-based dispensers connected to a syringe pump. The rejected phrases "the narrow opening of the tip", "the surface of the miniarray substrate" and "an action" have all been deleted.

Claim 9 has been amended to recite pipette-based dispensers arranged in one or two rows. Applicant submits that the claims have been amended to distinctly claim the subject matter of the present invention. Accordingly, Applicant respectfully requests that the rejections of claims 7 and 9-22 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 USC §102 Rejections

Claims 7, 9-10, 12-22 are rejected under 35 USC §102(e) as anticipated by **Balch** (U.S. Patent 6,083,763) or **Lockhart** et al. (U.S. Patent 6,040,138). This rejection is respectfully traversed.

The present invention provides the making and using of expression miniarrays – a novel category of biosensors that are intermediate in size, cost and ease of use between microarrays and macroarrays. Common laboratory macroarrays are usually hand made and only contain a few dozen spots per array. This macroarray format is not suitable for high throughput, high density analyses. On the other hand, microarray is a highly miniaturized, high density format that is expensive to make.

The miniarray of the present invention comprises assay spots that have a center-to-center spacing of about 0.5mm to about 3mm (page 24, line 17 to page 25, line 1; page 42, lines 3-11; Figure 3). In contrast, **Balch** or **Lockhart** et al. only teach microarray. **Balch** or **Lockhart** et al. do not teach or suggest miniarray of the present invention. **Balch** teaches a high density multiplexed system in which multiple test sites are deposited into each well of a microtiter plate. For example, a 4x4 matrix or a 15x15 array is deposited into each well of a 96-well microtiter plate (column 4, lines 43-52; column 6, lines 1-5). The

upper limit to the hybridization tests per microtiter plate exceeds 100,000 based on a 100 mm center-to-center spacing of biosites (column 6, lines 13-15).

Lockhart et al. teach a high density array comprising thousands or hundreds of thousands oligonucleotide probes (column 3, lines 7-20). Although **Lockhart** et al. do not specifically mention the center-to-center spacing of the oligonucleotide probes, one of skill in the art would readily recognize that in high density gene expression microarrays, the assay spots are typically 75 to 150 microns in diameter with center to center spacing of 100 to 375 microns (instant specification, page 5, lines 1-2). Similarly, the prior art of **Brown** et al. (U.S. Patent 5,807,522) teach microarray as having assay spots 10-250 um in diameter and separated from other assay spots in the array by about the same distance (column 6, lines 32-37). Hence, the high density microarrays of **Balch** or **Lockhart** et al. are different and distinct from the miniarray of the present invention. Since **Balch** or **Lockhart** et al. do not teach or suggest miniarray that comprises assay spots with a center-to-center spacing of about 0.5mm to about 3mm, **Balch** or **Lockhart** et al. do not anticipate claim 7 of the present application. Accordingly, Applicant respectfully requests that the rejection of claims 7, 9-10, 12-22 under 35 U.S.C. §102(e) be withdrawn.

Claims 7, 9-10, 12, 15, 16, 18-22 are rejected under 35 USC §102(b) as anticipated by **Brown** et al. (U.S. Patent 5,807,522). This rejection is traversed.

As discussed above, the present invention is drawn to a miniarray distinct from the microarrays of the prior art. The miniarray of the present invention comprises assay spots that have a center-to-center spacing of about 0.5mm to about 3mm. In contrast, **Brown** et al. teach microarray as having assay spots 10-250 μm in diameter and separated from other assay spots in the array by about the same distance (column 6, lines 32-37). **Brown** et al. also teach a microarray having assay spots 20-200 μm in diameter and a center-to-center spacing in the range of 20-400 μm (column 9, lines 30-40). Hence, the high density microarrays of **Brown** et al. is different and distinct from the miniarray of

the present invention. **Brown** et al. do not teach or suggest the miniarray of the present invention. Since **Brown** et al. do not teach or suggest each and every aspect of the present invention, **Brown** et al. do not anticipate claim 7 of the present application. Accordingly, Applicant respectfully requests that the rejection of claims 7, 9-10, 12, 15, 16, 18-22 under 35 U.S.C. §102(b) be withdrawn.

The 35 USC §103(a) Rejections

Claims 7 and 9-22 are rejected under 35 USC §103(a) as being unpatentable over any one of **Balch** or **Lockhart** or **Brown** in view of **Lange** (abstract). This rejection is respectfully traversed.

As discussed above, **Balch** or **Lockhart** or **Brown** et al. all teach high density microarrays. Lange teaches a contamination-free device for pipetting liquid, said device comprises a reusable dispensing element and a disposable double tip.

In contrast, the present invention is drawn to a miniarray distinct from the microarrays of the prior art. The miniarray is in a lower density format and is less expensive to make and easier to use than the high density microarrays of **Balch** or **Lockhart** or **Brown** et al. **Balch** or **Lockhart** or **Brown** et al. do not teach or suggest an array in a lower density format such as the miniarray of the present invention. In the absence of teaching that shows the feasibility and efficacy of miniarray, one of ordinary skill in the art would have no idea on the usefulness of miniarray as claimed in this application.

In view of the above remarks, the combined teaching of **Balch** or **Lockhart** or **Brown** in view of **Lange** do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicant's claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claims 7 and 9-22 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed March 13, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com